Diabetes and the endocrine heart

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Online publish-ahead-of-print 14 September 2007

This editorial refers to 'Diabetes-specific cardiomyopathy in type 1 diabetes mellitus: no evidence for its occurrence in the era of intensive insulin therapy' by E. Konduracka et al., on page 2465

Diabetes mellitus is a disease with major clinical relevance in the cardiological setting. Diabetes predisposes to atherosclerosis and myocardial damage often requiring acute cardiological intervention and long-term treatment. As the common type 2 form of diabetes can go undiagnosed for many years, cardiologists will often also be the first clinicians to diagnose the metabolic disorder in patients presenting with diabetes-related complications. Thus, primary diagnosis, initial treatment, and long-term glycaemic control of diabetes are all an integral part of cardiology.

B-type natriuretic peptide (BNP) and molecular fragments of its precursor (NT-proBNP) are useful plasma markers in cardiac disease.¹ Low plasma concentrations can exclude severe systolic cardiac dysfunction, whereas increased concentrations favour—but are not specific for—a diagnosis of heart failure. These markers also look promising in differentiating between cardiovascular and pulmonary causes of dyspnoea, and they contain general prognostic information, i.e. the higher the plasma concentration, the higher the risk for all-cause morbidity and death.

The troublesome lack of diagnostic specificity for the natriuretic peptide has almost become a research field of its own in the last few years. Some experts have accordingly defined a so-called ‘grey zone’, where the plasma concentrations are higher than ‘normal’ but lower than a set cut-off value for heart failure. Many factors besides systolic heart failure affect the plasma concentrations of proBNP-derived peptides, where age and gender are the easiest to identify. Others mechanisms leading to altered concentrations in the circulation can be more difficult to make clinical sense of, including body mass index, myocardial hypoxia, and, for that matter, dysfunction of other organs.

Konduracka et al.² report on diabetic cardiomyopathy in patients with type 1 diabetes. The study concludes that type 1 diabetes with modern insulin treatment (HBA1c = 7.5 ± 1.4%) is not associated with echocardiographic, biochemical, or morphological signs of diabetic cardiomyopathy. For instance, the NT-proBNP concentrations did not differ between the diabetic study group and an age-matched control group, although a significant correlation was found between NT-proBNP plasma concentrations and the duration of diabetes (which could simply be due to increasing age). Thus, the results fit well with our general contention that well treated type 1 diabetes does not impose an independent risk for the myocardium and corroborate the prevailing argument for strict glycaemic regulation in type 1 diabetes. In practical terms, an increased NT-proBNP plasma concentration in a patient with type 1 diabetes should be interpreted in the same way as an increased concentration in other patients, i.e. one must suspect heart failure.

The real challenge for the cardiac peptides seems to be more closely related to the common type 2 form of diabetes. The incidence of type 2 diabetes is expected to increase as a function of the increasing prevalence of obesity in the Western world. Moreover, type 2 diabetes often has a much longer undiagnosed time span (years) than type 1 diabetes. After diagnosis, it can even be difficult to achieve optimal glycaemic control. It is therefore reasonable to suspect that actual diabetic cardiomyopathy as an independent pathology should be suspected in this form of diabetes. Several hormones and tissues besides insulin and pancreatic β-cells are involved in the metabolic syndrome, including adipose tissue, liver, muscle (possibly including the heart itself), and the kidneys. Using proBNP-derived peptides as plasma markers in patients with type 2 diabetes can easily become a complex matter. For instance, obesity, an important risk factor for the disease itself, lowers the plasma concentrations of these peptides, whereas increasing age and coronary artery disease increase their concentration. Renal and hepatic changes may also affect the circulating concentrations. To complicate interpretation further, it could be suspected that anti-diabetic medicine directly or indirectly may affect the peptide concentrations; inhibition of DDP-IV (dipeptidyl-dipeptidase IV), an enzyme that degrades the incretin glucagon-like peptide 1, but also BNP-32, certainly will make the interpretation of BNP measurement tricky (Table 1). Clearly, we are still far from having meaningful cut-off values for proBNP-derived peptides in such high risk patients.

In 1972, Rubler et al. described patients with diabetes and heart failure without coronary artery disease or hypertension.³ Since then, it has been shown that patients with diabetes develop echocardiographic abnormalities related to
also support that leptin-associated type 2 diabetes leads to cardiac dysfunction in leptin receptor-deficient db/db mice. Studies of the hearts from control mice and display diastolic dysfunction, whereas non-obese diabetic (NOD) mice have reduced ANP mRNA levels in the heart. In parallel, streptozotocin-treated pigs display increased atrial but not ventricular BNP mRNA expression.

The combined lessons from these experimental studies on diabetes and diabetic cardiomyopathy should still be interpreted with caution. Chemically induced diabetes can hardly be said to represent the common human form of type 2 diabetes, and genetically modified rodents also differ greatly in respect to human-related long-term insulin resistance and β-cell dysfunction. An interesting yet relatively unexplored perspective is diabetes in small domestic animals, where cats and dogs display both type 2 and type 1 diabetes resembling the human disease. These natural animal models almost mimic the human disease in time of onset, long-term duration, and even anti-diabetic treatment, although the glycaemic control is generally much less stringent. Finally, small animals do not develop coronary artery disease, which would make interpretation of a diabetes-related cardiac pathology easier. Of note, it has recently been proposed that studies in natural animal models may provide important contributions to our understanding of human disease.

Perhaps the most interesting aspect of proBNP-derived peptides in diabetes could be their potential role as active hormones implicated in the metabolic syndrome (Figure 1). Adipose tissue and the heart itself express receptors for the natriuretic peptides. It has been shown that BNP (and ANP) possesses important lipolytic effects in animals. Moreover, BNP has antifibrotic effects on the heart muscle. In a recent epidemiological study, it was shown that a genetic polymorphism in the BNP promoter is associated with increased BNP gene expression and higher plasma concentrations, lower blood glucose levels, and lower risk for type 2 diabetes. While this new information still needs to be explored in detail, it is important to bear in mind that high circulating BNP concentrations on one hand might be undesirable for the patient in the context of clinical prognosis and diagnosis. On the other hand, increased BNP concentrations may be an important biological feature of the endocrine heart in protecting against inflammatory, metabolic, and other activated mechanisms leading to cardiac fibrosis. Thus, the endocrine heart may not just be an innocent victim in diabetes but...
rather intricately involved in the metabolic syndrome. The cardiac ability to mount an appropriate BNP response in long-term diabetes might therefore be ‘a good thing’ for the individual patient.

Conflict of interest: none declared.

References